PFIZER INC., 235 EAST 42nd STREET, NEW YORK, N. Y. 10017

GERALD D. LAUBACH, Ph. D.
President

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Professor Joshua Lederberg
Department of Genetics
School of Medicine
Stanford University
Stanford, California 94305

Dear Professor Lederberg:

Please excuse my delay in replying to your recent note. I have been away in Europe on business and vacation and only now am catching up with my correspondence.

I am not sure I understand from your very brief note the full thrust of the hypothesis you are developing in the paper you mention, or what kind of information we might have that would be helpful to you. However, I have enclosed some papers we have done that may be relevant (on the chance you have not seen them already). If you can identify additional kinds of material we might supply, please let me know.

Dr. Gilgore's papers deal with what we believe to be one factor that has influenced the obviously variable "batting averages" before the FDA. This factor - namely the approach used in the development and presentation of data about a new drug - is probably less a variable now than it was in the earlier years under the Drug Amendments of '62. During those earlier years, we strongly suspect that drug development organizations did vary in their rate of transition to the more demanding, exhaustive, and sophisticated programs that are now obviously required to convince FDA of the safety and effectiveness of a new drug.

Barry Bloom's paper, which you may know about since it was presented in part at Stanford, discusses another significant factor in the variable outcome of new drug petitions, namely that some classes of drugs have been consistently handled by FDA much more constructively than others. Although there is some technical rationale for such differences, the inference is overwhelming that the dominant factor has been the differing attitudes about new drugs and the drug industry that prevail within different reviewing groups in the FDA. As I am sure you appreciate, the amount and nature of evidence that will be accepted as sufficient demonstration of safety and effectiveness to permit new drug approval is highly subjective, nowhere specifically defined in operational terms in the statutes or regulations. Hence, the quantum of proof required to win approval has almost certainly varied drastically from reviewer to reviewer and drug classification to drug classification.

One implication from this is one's "batting average" can be influenced by the field of therapeutics one elects to research. There is considerable empirical evidence that this fact has influenced research policy. Carl Djerassi's view relating to the outlook for oral contraceptives research is only the extreme example of this kind of thing.

With regard to the final point raised in your note - has there been unrealistic optimism in the expectations for therapeutic research productivity? I can think of nothing from our experience that is really relevant to this proposition. Based on our experience, we have for a number of years planned on a very substantial failure rate of our experimental drugs. Most of these failures take place in the earlier stages of animal safety and clinical testing, and the loss of candidates after completion of Phase II clinical trials has been a rarity. We have not seen a trend that has caused us to change our anticipated failure rate over the last eight to ten years.

In any event, I believe that the more influential factor in the attitudes of industry research people about the present state of affairs, is not so much the late stage failures in product development, but rather the lengthy and largely irrational delays that have become integral in drug development and the regulatory review process. Certainly this is the central theme of our concern.

The fact is that every New Drug Application we have submitted in recent time has been approved, but I believe an objective observer would be truly hard put to rationalize the time course of the process involved, nor some of the specific events that were the source of substantial delay. This aspect of the issue is, to me, one of the most vexing of all, in part because I fail to understand how anyone with any knowledge of the nature of the behavior of bureaucracies, and particularly a bureaucracy subject to powerful negative pressures, can fail to appreciate a priori that this must be a major consideration influencing the development of new therapeutic agents in our society today.

Best regards.

Sincerely,

G. D. Laubach

Att.